HFA-305, Dockets Management Branch

DATE OF APPROVAL LETTER JUN 21 2000

FREEDOM OF INFORMATION SUMMARY

Out of specification label change for IVOMEC® SR Bolus for Cattle

I. GENERAL INFORMATION

NADA NUMBER:	140-988
SPONSOR:	Merial Limited 2100 Ronson Road Iselin, New Jersey 08830-3077
GENERIC NAME:	Ivermectin
TRADE NAME:	IVOMEC® SR Bolus for Cattle
DOSAGE FORM:	sustained-release bolus
MARKETING STATUS:	OTC in cattle, one bolus per 275-600 pounds on the day of administration
PHARMACOLOGIC CATEGORY:	Antiparasitic
EFFECT OF SUPPLEMENT:	This supplement provides for the revision of 21 CFR 520.1197(d)(2) by replacing "(approximately 135 days)" with "(approximately 130 days)" for the ivermectin delivery period.

II. INDICATIONS FOR USE

NEMATODES

The IVOMEC® SR Bolus is indicated for the treatment of established infections and, throughout its approximately 130-day ivermectin delivery period, controls the establishment of infection by newly ingested larvae of the following nematode species:

Gastrointestinal Roundworms

Haemonchus placei
Ostertagia ostertagi
Trichostrongylus axei
Trichostrongylus colubriformis
Cooperia spp.

FOIS 1

Nematodirus helvetianus
Bunostomum phlebotomum
Oesophagostomum radiatum

Lungworms
Dictyocaulus viviparus

IVOMEC® SR Bolus controls established infections with hypobiotic (inhibited) fourth-stage larvae of *Ostertagia ostertagi*.

MANGE MITES
The IVOMEC® SR Bolus provides control of established infestations of the following mange mites and prevents reinfestation for 130 days.
Psoroptes ovis
Sarcoptes scabiei

SUCKING LICE
The IVOMEC® SR Bolus provides control of established infestations of the following sucking lice and prevents reinfestation for 130 days.
Linognathus vituli
Solenopotes capillatus

CATTLE GRUBS
Initially, control is provided against migrating *Hypoderma* larvae or grubs acquired prior to administration of the IVOMEC SR Bolus; thereafter, prophylaxis is provided for approximately 130-days against newly acquired larvae.
Hypoderma spp

TICKS
Control of the following tick will be provided by interfering with engorgement with blood and completion of the reproductive portion of the life cycle by newly acquired young adult females during the period of ivermectin delivery. However, larvae, nymphs and adult males, as well as young adult females already on the host at the time of treatment and actively in the engorgement process, may not be visibly affected.
Amblyomma americanum

III. DOSAGE

A. Dosage Form: sustained-release bolus

B. Route of Administration: oral

C. Recommended Dosage: One bolus (containing 1.72 g ivermectin) is to be given orally to cattle at least 12 weeks of age and weighing 275 lb (125 kg) to 660 lb. (300 kg) body weight on the day of administration. Each bolus is formulated to deliver 12 mg of ivermectin/day for 130 days.

IV. EFFECTIVENESS

Effectiveness in cattle was established originally under NADA 140-988. No additional data were required for approval of this supplement. Due to the increased amount of stability data now available, it is necessary to decrease the predicted lifetime specification for the IVOMEC SR Bolus. When the original lifetime prediction model was developed, only a limited body of knowledge was available concerning the effect of sample age on the predicted lifetime. Now that additional data are available through the 24-month expiry, a more appropriate shelf-life specification is proposed. The shelf-life specification was lowered from 116.5-152.1 days to 109.4-145.0 days. The ivermectin delivery period at release was then decreased from 116.5-152.1 days to 116.5-145.0 days. The label was modified to reflect this change from an ivermectin delivery period of "approximately 135-days" to "approximately 130-days".

V. TARGET ANIMAL SAFETY

Animal safety in cattle was established originally under NADA 140-988. No additional data were required for approval of this supplement.

VI. HUMAN FOOD SAFETY

As discussed in the parent NADA 140-988 FOI Summary (approval date November 18, 1996). For a complete summary of the toxicity tests for ivermectin, please consult the FOI Summary for NADA 128-409, IVOMEC® (ivermectin) 1% Injection for Cattle.

VII. AGENCY CONCLUSIONS

The information submitted in support of this supplemental application satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations to revise 21 CFR 520.1197(d)(2) to reduce the period of protection from approximately 135 to approximately 130 days. All the other original indications remain the same.

There are no changes to the codified tolerances for ivermectin in cattle or to the established pre-slaughter withdrawal time of 120 days.

The Agency has concluded that this product shall retain over-the-counter marketing status because adequate directions for use have been written for the layman and the conditions for use prescribed on the label are likely to be followed in practice.

In accordance with 21 CFR 514.106(b)(2), this is a Category II change which did not require a reevaluation of the safety or effectiveness data in the parent application.

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for food producing animals does not qualifies for marketing exclusivity because the supplemental application does not contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant.

The agency has determined under 21 CFR 25.33(a)(1) that this action is of a type that does not individually or cumulatively have a significant impact on human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IVOMEC® SR Bolus for cattle is under U.S. patent numbers:

Patent Number	Expiration Date
4327725	November 30, 2000
4595583	March 19, 2004
4684524	June 17, 2003
4692336	June 17, 2003
4704118	August 16, 2005
4717568	May 1, 2005
4717718	June 17, 2003
4729793	March 8, 2005
4772474	June 12, 2003
4844984	June 17, 2003
4927633	June 17, 2003
4966767	October 30, 2007
5000957	June 17, 2003
5122128	June 16, 2009
5206024	April 27, 2010
5223266	June 29, 2010
5368863	June 29, 2010
5372776	December 13, 2001
5417976	April 27, 2010
5431919	June 23, 2013
5474785	July 20, 2010
5607696	February 10, 2015

VIII. APPROVED LABELING (Attached)

1. Bolus label
2. 12x Carton
3. Package Insert
4. 72x Carton

Product 41313

Ivomec® SR Bolus for Cattle

(ivermectin)

Each Bolus contains 1.72 g Ivermectin.

Indications: For control of gastrointestinal roundworms, lungworms, mange mites, sucking lice, cattle grubs and ticks. Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.

Recommended Use: One IVOMEC SR Bolus per calf weighing at least 275 lb (125 kg) and not more than 660 lb (300 kg) on the day of administration. Calves must be ruminating and greater than 12 weeks of age.

Contraindications: Do not administer to calves weighing less than 275 lb (125 kg). Administration to calves weighing less than 275 lb (125 kg) may result in esophageal injuries including obstruction or perforation with associated complications, including fatalities.

Not for human use. Keep this and all drugs out of the reach of children. Wash hands after use.

RESIDUE INFORMATION: Do not slaughter within 180 days of treatment (day of administration). Because a milk withdrawal time has not been established, do not use in female dairy cattle of breeding age.

Remove each bolus from its container only immediately prior to use.

To administer, use a balling gun that will deliver the IVOMEC SR Bolus into the pharynx. Do not use excessive force. Do not administer a damaged bolus. **See package insert for complete indications and directions.**

Storage Conditions: Store below 86°F/30°C; protect from excessive heat 104°F/40°C.

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Merial Limited, 2100 Ronson Road,
Iselin, NJ 08830-3077, USA

MERIAL

Lot & Exp Date ▶

Product 41313

Ivomec®

(ivermectin)

SR Bolus

for Cattle

NADA 140-988,
Approved by FDA

Parasiticide

Each Bolus Contains
1.72 g Ivermectin

Sustained-release bolus for the control of internal and external parasites of cattle

Package contains Twelve Boluses

MERIAL

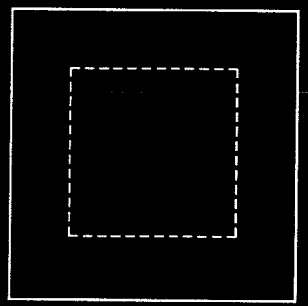
Product 41313

Ivomec® SR Bolus

(ivermectin) for Cattle

Parasiticide

Each Bolus Contains 1.72 g Ivermectin



Package contains
Twelve Boluses

Product 4313

Parasiticide

INDICATIONS: The IVOMEC SR Bolus is indicated for the treatment of internal and external parasites in cattle throughout the grazing season.

Gastrointestinal Roundworms: *Haemonchus placei*, *Ostertagia ostertagi* (including hypobiotic fourth-stage larvae), *Trichostrongylus axei*, *T. colubriformis*, *Cooperia* spp., *Nematodirus helvetianus*, *Bunostomum phlebotomum*, *Oesophagostomum radiatum*

Lungworms: *Dictyocaulus viviparus*

Mange Mites: *Psoroptes ovis*, *Sarcoptes scabiei*

Sucking Lice: *Linognathus vituli*, *Solenopotes capillatus*

Cattle Grubs: *Hypoderma* spp.

Ticks: *Amblyomma americanum*

Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.

See package insert for complete indications and directions.

CONTRAINDICATIONS: The IVOMEC SR Bolus is specifically formulated for the use in calves 275 - 660 lb (125-300 kg) body weight on the day of bolus administration. Calves must be ruminating and greater than 12 weeks of age. **Do not administer to calves weighing less than 275 lb (125 kg).** Administration to calves weighing less than 275 lb (125 kg) may result in esophageal injuries including obstruction or perforation with associated complications, including fatalities.

WARNING: Not for human use. Keep out of reach of children. Wash hands after use. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users, to obtain more information, or to obtain a MSDS, contact Merial at 1-888-637-4251.

TAKE TIME

OBSERVE LABEL DIRECTIONS

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Lot No & Exp Date ▼

RESIDUE INFORMATION: Do not slaughter cattle within 180 days of treatment (day of administration). Because a milk withdrawal time has not been established, do not use in female dairy cattle of breeding age.

PRECAUTIONS:

REMOVE EACH BOLUS FROM ITS CONTAINER ONLY IMMEDIATELY PRIOR TO USE.

Do not administer a damaged bolus.

The IVOMEC SR Bolus was specifically designed for use in cattle, and is not intended for use in other animal species.

Avoid using excessive force during administration.

Only a balling gun which has suitable dimensions and will deliver the IVOMEC SR Bolus into the pharynx should be used for administration. Instruments intended for administration of other types of boluses may result in delivery into the oral cavity and the teeth may cause damage to the bolus.

Environmental Safety: Damaged boluses should be disposed of safely (e.g. by burying at an approved landfill or incinerating). Do not contaminate lakes, streams or ground water.

DOSAGE: One IVOMEC SR Bolus per calf weighing at least 275 lb (125 kg) and not more than 660 lb (300 kg) body weight on the day of administration. Calves must be ruminating and greater than 12 weeks of age. Each bolus contains 1.72 g vermectin.

STORAGE CONDITIONS: Store below 86 F/30 C. Protect from excessive heat (104 F/40 C). The IVOMEC SR Bolus is stable for two years when stored below 86 F/30 C.

Merial Limited
2100 Ronson Road, Iselin, NJ 08830-3077, USA

NADA 140-988, Approved by the FDA 7999503F

Ivomec® SR Bolus for Cattle

(Ivermectin)

INTRODUCTION

The IVOMEC® (ivermectin) Sustained Release (SR) Bolus controls internal and external parasites in cattle throughout the grazing season. The IVOMEC SR Bolus contains ivermectin, a unique chemical entity discovered and developed by scientists from Merck Research Laboratories.

MODE OF ACTION

Ivermectin is a member of the macrocyclic lactone class of endectocides which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells.

This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

The wide margin of safety is attributable to the fact that mammals do not have glutamate-gated chloride channels, the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood-brain barrier.

INDICATIONS

Nematodes

The IVOMEC SR Bolus is indicated for the treatment of established infections and, throughout its approximately 130 day ivermectin delivery period, prevents the establishment of infection by newly ingested larvae of the following nematode species:

Gastrointestinal Roundworms

- *Haemonchus placei*
- *Ostertagia ostertagi*
- *Trichostrongylus axei*
- *Trichostrongylus colubriformis*
- *Cooperia* spp.
- *Nematodirus helvetianus*
- *Bunostomum phlebotomum*
- *Oesophagostomum radiatum*

Lungworms

- *Dictyocaulus viviparus*

IVOMEC SR Bolus controls established infections with hypobiotic (inhibited) fourth-stage larvae of *Ostertagia ostertagi*.

Mange Mites

The IVOMEC SR Bolus provides control of established infestations of the following mange mites and prevents reinfestation for 130 days.

- *Psoroptes ovis*
- *Sarcoptes scabiei*

Sucking Lice

The IVOMEC SR Bolus provides control of established infestations of the following sucking lice and prevents reinfestation for 130 days.

- *Linognathus vituli*
- *Solenopotes capillatus*

Cattle Grubs

Initially, control is provided against migrating *Hypoderma* larvae (grubs) acquired prior to administration of the IVOMEC SR Bolus; thereafter, prophylaxis is provided for approximately 130 days against newly acquired larvae.

- *Hypoderma* spp.

Ticks

Control of the following tick will be provided by interfering with engorgement with blood and completion of the reproductive portion of the life cycle by newly acquired young adult females during the period of ivermectin delivery. However, larvae, nymphs and adult males, as well as young adult females already on the host at the time of treatment and actively in the engorgement process, may not be visibly affected.

- *Amblyomma americanum*

ANIMAL SAFETY

In a study to investigate the effects of exaggerated doses of ivermectin administered via multiple boluses, groups of 6 calves weighing 142 to 200 kg were treated with ivermectin administered by SR bolus at (1X), (3X) or (5X) the therapeutic dose. Between one and 6 SR boluses were administered to each animal to deliver the assigned dose level of ivermectin. Mild digestive disturbances were observed in some calves given 3 or more boluses and calves in the groups treated at 3X and 5X gained less weight than untreated controls. These signs were attributed to effects from the physical mass of multiple devices in the rumen. Mild symmetrical mydriasis was observed in 4 of the 6 calves treated at 3X dose and in 2 of the 6 calves treated at 5X dose and one calf treated at 3X dose showed mild depression. No other clinical signs were observed during the study.

The effects of ivermectin sustained release bolus on reproductive performance in breeding bulls and cows have not been evaluated. However, the injectable ivermectin formulation (immediate release) had no effects on reproductive performance in studies in breeding bulls and cows.

CONTRAINDICATIONS

The IVOMEC (ivermectin) SR Bolus is specifically formulated for use in calves 275-660 lb (125-300 kg) body weight on the day of bolus administration. Calves must be ruminating and greater than 12 weeks of age. **Do not administer in calves weighing less than 275 lb (125 kg).** Administration to calves weighing less than 275 lb (125 kg) may result in esophageal injuries including obstruction or perforation with associated complications, including fatalities.

WARNING

Not for human use.

Keep out of reach of children.

Wash hands after use. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users, to obtain more information, or to obtain a MSDS, contact Merial at 1-888-637-4251.

RESIDUE INFORMATION: Do not slaughter cattle within 180 days of treatment (day of administration). Because a milk withdrawal time has not been established, do not use in female dairy cattle of breeding age.

PRECAUTIONS

Remove each bolus from its container only immediately prior to use.

Do not administer a damaged bolus.

The IVOMEC SR Bolus was specifically designed for use in cattle, and is not intended for use in other animal species.

Avoid using excessive force during administration.

Only a balling gun which has suitable dimensions and will deliver the IVOMEC SR Bolus into the pharynx should be used for administration. Instruments intended for administration of other types of boluses may result in delivery into the oral cavity and the teeth may cause damage to the bolus.

Environmental Safety

Studies indicate that when ivermectin comes in contact with the soil, it readily and tightly binds to the soil and becomes inactive over time. Free ivermectin may adversely affect fish and certain water-borne organisms on which they feed. Damaged boluses should be disposed of safely (e.g., by burying at an approved landfill or incinerating). Do not contaminate lakes, streams or ground water.

Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.

DOSAGE AND ADMINISTRATION

One IVOMEC SR Bolus is given to cattle weighing at least 275 lb (125 kg) and not more than 660 lb (300 kg) body weight on the day of administration. Calves must be ruminating and greater than 12 weeks of age. Each bolus contains 1.72 g ivermectin.

Care should be exercised in handling and administering the IVOMEC SR Bolus to ensure that the outer membrane is not damaged. Administer the bolus directly into the pharynx using an appropriate balling gun.

Remove the bolus from the container and insert into the retaining cup of the balling gun.

Place the instrument centrally into the animal's mouth just beyond the back of the tongue (i.e. pharynx) using gentle pressure and allowing the animal to swallow. Release the bolus by slowly depressing the plunger or trigger. If there is any resistance to release of the bolus, reposition the bolus cup.

Following release of the bolus, withdraw the balling gun. Once swallowed, the IVOMEC SR Bolus has sufficient density to be retained in the rumen/reticulum for an extended duration. Some calves may not successfully complete the swallowing reflex upon initial administration; observe each animal briefly prior to release. Regurgitation of the bolus, although infrequent, has been observed during the first day after administration and throughout the delivery period.

STORAGE CONDITIONS

Store below 86°F/30°C. Protect from excessive heat (104°F/40°C). The IVOMEC SR Bolus is stable for two years when stored below 86°F/30°C.

HOW SUPPLIED

IVOMEC SR Bolus (Product 41313) is available containing 1.72 g of ivermectin and packaged 12 boluses per carton or 72 boluses per carton.

Merial Limited
2100 Ronson Road
Iselin, NJ 08830-3077, USA

 September 1999

MERIAL

20.375"

UPC Bar Code

Product 41313

Package contains 72 Boluses

GMP Bar Code

Ivomec® SR Bolus for Cattle

(ivermectin)

Ivomec® SR Bolus for Cattle

(ivermectin)

Package contains 72 Boluses

Product 41313

Product 41313

Ivomec® SR Bolus for Cattle

(ivermectin)

NADA 140-988, Approved by the FDA

Parasiticide

Each Bolus Contains 1.72 g Ivermectin

Sustained-release bolus for the control of internal and external parasites of cattle

MERIAL

Package contains 72 Boluses

Ivomec® SR Bolus for Cattle

Ivomec®
(ivermectin)

SR Bolus
for Cattle

Parasiticide

INDICATIONS: The IVOMEC SR Bolus is indicated for the treatment of internal and external parasites in cattle throughout the grazing season.

Gastrointestinal Roundworms: *Haemonchus placei, Ostertagia ostertagi* (including hypobiotic fourth-stage larvae), *Trichostrongylus axei, T. colubriformis, Cooperia* spp., *Nematodirus helvetianus, Bunostomum phlebotomum, Oesophagostomum radiatum*
Lungworms: *Dictyocaulus viviparus*
Mange Mites: *Psoroptes ovis, Sarcoptes scabiei*
Sucking Lice: *Linognathus vituli, Solenopotes capillatus*
Cattle Grubs: *Hypoderma* spp.
Ticks: *Amblyomma americanum*

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Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.
See package insert for complete indications and directions.

CONTRAINDICATIONS: The IVOMEC (ivermectin) SR Bolus is specifically formulated for the use in calves 275 - 660 lb (125-300 kg) body weight on the day of bolus administration. Calves must be ruminating and greater than 12 weeks of age. **Do not administer to calves weighing less than 275 lb (125 kg).** Administration to calves weighing less than 275 lb (125 kg) may result in esophageal injuries including obstruction or perforation with associated complications, including fatalities.

WARNING: Not for human use. Keep out of reach of children. Wash hands after use. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users, to obtain more information, or to obtain a MSDS, contact Merial at 1-888-637-4251.

RESIDUE INFORMATION: Do not slaughter cattle within 180 days of treatment (day of administration). Because a milk withdrawal time has not been established, do not use in female dairy cattle of breeding age.

PRECAUTIONS:

REMOVE EACH BOLUS FROM ITS CONTAINER ONLY IMMEDIATELY PRIOR TO USE.

Do not administer a damaged bolus.
The IVOMEC SR Bolus was specifically designed for use in cattle, and is not intended for use in other animal species.

Avoid using excessive force during administration.
Only a balling gun which has suitable dimensions and will deliver the IVOMEC (ivermectin) SR Bolus into the pharynx should be used for administration. Instruments intended for administration of other types of boluses may result in delivery into the oral cavity and the teeth may cause damage to the bolus.

Environmental Safety: Damaged boluses should be disposed of safely (e.g. by burying at an approved landfill or incinerating). Do not contaminate lakes, streams or ground water.

DOSAGE: One IVOMEC SR Bolus per calf weighing at least 275 lb (125 kg) and not more than 660 lb (300 kg) body weight on the day of administration. Calves must be ruminating and greater than 12 weeks of age. Each bolus contains 1.72 g ivermectin.

STORAGE CONDITIONS: Store below 86°F/30°C. Protect from excessive heat (104°F/40°C). The IVOMEC SR Bolus is stable for two years when stored below 86°F/30°C.

Lot No & Exp Date ▶

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2100 Ronson Road
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